DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Deciphering the Role of Putrescine in Host-pathogen Interaction in Shigella Infection

Supervisor: Gianni Prosseda

Email: gianni.prosseda@uniroma1.it

Website: https://corsidilaurea.uniroma1.it/it/users/gianniprossedauniroma1it

Summary

The research proposed is focused on the role of putrescine in the interaction between host cells and *Shigella*, the etiological agent of human bacillary known as shigellosis. This bacterial pathogen can translocate from the intestinal lumen to the submucosa side where it is intercepted by the resident macrophages which engulf it. This process triggers pyroptosis, a form of cell death of infected macrophages, accompanied by the release of pro-inflammatory cytokines. *Shigella* then utilizes type III secretion systems (T3SS) to invade epithelial cells and spread within the intestinal mucosa (Haidar-Ahmad et al., 2023). Polyamines, including putrescine, cadaverine, and spermidine, are small molecules ubiquitous in all living cells. They play crucial roles in various cellular processes because of their ability to act as polycations, interacting with nucleic acids, proteins, and cell membranes (Tabor and Tabor, 1984; Pegg et al., 2011). Polyamines are important in cell physiology due to their influence on several processes such as transcription, translation, stress response, and virulence. Pathogens such as *Helicobacter pylori*, *Salmonella* Typhimurium, and *Edwardsiella piscicida* manipulate host polyamine metabolism to modulate the immune response, resist oxidative stress, or influence cellular functions to improve their survival and virulence (Lewis et al., 2011; Chaturvedi et al. 2014; Chiang and Schellhorn, 2012; Nair et al., 2023; Jiang et al., 2021).
Recent findings indicate that *Shigella* releases putrescine into the macrophage cytoplasm during the invasion, contributing to the induction of pyroptosis (Pasqua et al., in prep) and helping *Shigella* to evade host immune defences. The objectives of this research project are to decipher the molecular mechanisms through which the released putrescine promotes pyroptosis in macrophages and to identify and characterize further possible pathogen-dependent reshaping of the host polyamine metabolism. The expected results will further emphasize the importance of polyamines, particularly putrescine, in host-pathogen interaction during Shigella infections, confirming that manipulation of polyamine metabolism by pathogens represents a sophisticated strategy to enhance their fitness and optimize virulence. Understanding these interactions provides insight into novel therapeutic targets and strategies to combat bacterial infections effectively.

Pertinent Publications of the proponent (last 5 years)

1. Diffusible signal factors (DSFs) bind and repress VirF, the leading virulence activator of Shigella flexneri.Trirocco R, Pasqua M, Tramonti A, Colonna B, Paiardini A, Prosseda G. Sci Rep. 2023 Aug 14;13(1):13170. doi: 10.1038/s41598-023-40023-w.PMID: 37580399 Free PMC article.
2. Role of the MDR Efflux Pump AcrAB in Epithelial Cell Invasion by Shigella flexneri. Coluccia M, Béranger A, Trirocco R, Fanelli G, Zanzi F, Colonna B, Grossi M, Prosseda G, Pasqua M. Biomolecules. 2023 May 11;13(5):823. doi: 10.3390/biom13050823. PMID: 37238693 Free PMC article.
3. Fatty Acids Abolish Shigella Virulence by Inhibiting Its Master Regulator, VirF. Trirocco R, Pasqua M, Tramonti A, Grossi M, Colonna B, Paiardini A, Prosseda G. Microbiol Spectr. 2023 Jun 15;11(3):e0077823. doi: 10.1128/spectrum.00778-23. Epub 2023 May 4. PMID: 37140433 Free PMC article.
4. Roles of Two-Component Signal Transduction Systems in Shigella Virulence. Pasqua M, Coluccia M, Eguchi Y, Okajima T, Grossi M, Prosseda G, Utsumi R, Colonna B. Biomolecules. 2022 Sep 18;12(9):1321. doi: 10.3390/biom12091321. PMID: 36139160 Free PMC article. Review.
5. The MFS efflux pump EmrKY contributes to the survival of Shigella within macrophages. Pasqua M, Grossi M, Scinicariello S, Aussel L, Barras F, Colonna B, Prosseda G. Sci Rep. 2019 Feb 27;9(1):2906. doi: 10.1038/s41598-019-39749-3. PMID: 30814604 Free PMC article.

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